American Journal of Hematology 51:90–92 (1996)

High-Dose Intravenous Desferrioxamine (DFO) Delivery in Four Thalassemic Patients Allergic to Subcutaneous DFO Administration

Turiddu Lombardo, Gabriella Ferro, Viviana Frontini, and Sebastiano Percolla

Servizio Talassemia, Ospedale Ferrarotto USL 35 Catania, Italy (T.L., G.F., V.F.); Unità Nutrizionale, Clinica Specializzata Gretter, Catania, Italy (S.P.)

To test the hypothesis that allergy to desferrioxamine is not an immunologic mechanism, but arises from a local effect on the dermal mast cell, we have treated four patients who were not receiving chelation therapy because of hypersensitivity to standard subcutaneous (SC) therapy, with high-dose desferrioxamine (DFO) by the intravenous (IV) route. Three patients had central venous access ports implanted on the anterior chest wall. The fourth patient had the therapy delivered by the peripheral vein route. All patients had the drug delivered via an elastomeric infusor. Intravenous therapy was successful for all patients. During one year of therapy no local or systemic allergic manifestations were noted. In addition, no impairment of hearing or vision or any catheter complications were reported. A very high level of patient compliance to the therapy resulted in dramatically decreased iron stores and ferritin levels (2,759 ng/ml to 717.5 ng/ml) and a significant improvement in the clinical status of all patients. The absence of allergic episodes in this patient group after 1 year of IV therapy would strongly support the hypothesis that SC DFO allergy is related to a direct effect on dermal mast cells and is not an immunological reaction. This study suggests that patients with severe allergy to SC DFO can therefore safely receive their chelation therapy via the IV route. © 1996 Wiley-Liss, Inc.

Key words: desferrioxamine (DFO), thalassemia, allergy to subcutaneous DFO, iron overload, high-dose infusion chelating therapy

INTRODUCTION

Desferrioxamine (DFO), when regularly administered by subcutaneous (SC) or intravenous (IV) infusion, is still today the only preventive and curative treatment of post-transfusional hemocromatosis [1,2]. Patients who are unable to receive chelation therapy because of hypersensitivity to the standard SC route accumulate very large iron stores, have a poor quality of life, and are at serious or even fatal risk of iron-induced organ damage [3–7]. Recent studies indicate that DFO does not stimulate human basophils but induces a direct, nonimmunologic activation of the dermal mast cells (MC). These findings indicate that DFO has a direct IgE-independent stimulatory effect on connective tissue [8]. In patients in whom allergic symptoms to DFO develop, no specific IgE or IgG antibodies against DFO are detected [9].

These results led us to believe that these patients could safely tolerate IV DFO without risk of allergic reaction. In order to examine this hypothesis, we evaluated the IV administration of DFO in four thalassemic patients who were not receiving chelation therapy because of severe allergic reaction to SC administration.

METHODS

Four patients (two male and two female, aged 14–42 years) with a history of allergic manifestations from SC DFO participated in the study. Two patients, both with Thalassemia Intermedia, were transfusion non dependent. Two patients, one with thalassemia maior, and the other with sickle/thalassemia, were transfusion dependent. Patients 1, 2, and 3 demonstrated a very severe allergic reaction to SC DFO characterized by erythema, headache,

Received for publication May 10, 1995; accepted June 14, 1995.

Address reprint requests to Turiddu Lombardo, M.D., Servizio Talassemia Ospedale Ferrarotto USL 35, Via Citelli 6, 95124 Catania, Italy.

TABLE I. Patients' Clinical Data

Patient	Age	Weight (kg)	Sex	Diagnosis	Hb[a] (g/dl)	Transf. therapy[b]	Serum ferritin[c] (ng/ml)	ALT (IU/L)
01	22	55	M	Cooley	9.5	458	2,500	170
02	14	30	M	Th.Drepano	9.0	108	3,296	73
03	29	58	F	Th.Int	8.7	15	2,700	99
04	43	61	F	Th.Int.	9.1	04	2,540	173

[a]Mean pretransfusional Hb of the last 2 years.
[b]Units in the last 10 years.
[c]Mean of the last 2 years.

fever, tachypnea, and hypotension, bordering on an acute anaphylactic episode. By contrast, in patient 4, there were severe local allergic signs, including acute inflammation and painful oedematous swelling at the site of the SC infusion. We tried to desensitize the patients, but all desensitization treatments were unsuccessful. We also attempted chelation using saline but, as the method is cumbersome, there was a very poor compliance with this method. Our continued failure to find a satisfactory and safe method of delivering DFO subcutaneously meant that our patients were continuing to accumulate excess iron and began to demonstrate the development of iron-induced organ disease. Table I shows the clinical status and iron store in the patients prior to the study.

Patients were fully briefed on the objectives and reasons for the study and informed consent was obtained. We adopted a regimen of high-dose IV DFO for the four selected patients. To facilitate continuous access for the IV DFO, patients 1, 2, and 3 had a venous access port (Porth-A-Cath Pharmacia, Cologno M., Italy and Implantofix Braun, Milano, Italy) placed in a subcutaneous pocket in the anterior chest wall and running into the external subclavian vein. Patient 4 refused the implantable venous access; DFO therapy was provided in the peripheral vein. Each patient received 40 mg/kg DFO daily for 5 days during the first week; 50 mg/kg in the second week, and finally, the standard dose of 70 mg/kg. The daily dose of DFO was diluted in 40 ml water for injection, and introduced in to the reservoir of the disposable external device (Infusor 5 ml/hr. Baxter Healthcare Corp., Deerfield, IL, USA). When the reservoir is filled and the Infusor connected to a port, it operates with an internal pressure and provides continuous flow of the drug over 12 hr. It has no mechanical device or battery. The first administrations were performed inhospital; each patient then continued therapy at home.

Initially the patients were in close contact with medical staff in the event that any clinical problems might arise. As no problems were observed, we moved to a program of clinical visits and laboratory tests every 2 weeks. At the clinical visit, a 2 weeks supply of Infusor were handed to the patients for self-therapy at home.

RESULTS

After 1 year of therapy, no manifestations of local or systemic allergic reactions appeared. Serum ferritin levels, markedly elevated before the beginning of high-dose chelation therapy, fell dramatically. Mean ferritin concentration decreased from 2,759 ng/ml to 717.5 ng/ml (Fig. 1). The mean percentage decrease in ferritin was 73.75%. All patients had persistently elevated ALT levels (72–173 U/L) before intravenous therapy. These levels decreased in parallel with ferritin level, and the values reached were normal. The therapy removed excessive iron stores and the patient's awareness of early improvement in tests of iron status promote a better compliance and a psychological benefit. Patient 1, in whom an arrhythmia had developed related to iron overload returned to sinus rhythm. All patients initially had dark bronze-colored skin, but during therapy they gradually regained a fair complexion. No patients reported impairment of hearing or vision. No catheter complications were observed. The highest level of the compliance was experienced.

CONCLUSIONS

We have treated four patients, who were not previously receiving chelation therapy because they were allergic to standard sc DFO therapy, with high doses of DFO by Infusor 5 ml/hr. Our study has shown that patients with severe allergic reaction to DFO administered by the SC route, can receive their therapy by the IV route without risk of systemic allergic reaction. The success of this method of chelation improved the iron tests, and general conditions and promoted a better compliance. These results support the hypothesis of Shalit et al. [8] that sc DFO allergy is related to stimulation of the dermal mast cell and is IgE independent. The marked improvement in patients' ferritin levels, the absence of allergic episodes after 1 year of therapy, the absence of port complications, and the very high patient compliance, with enhanced quality of life, support the selection of the IV route in cases of allergy to SC DFO.

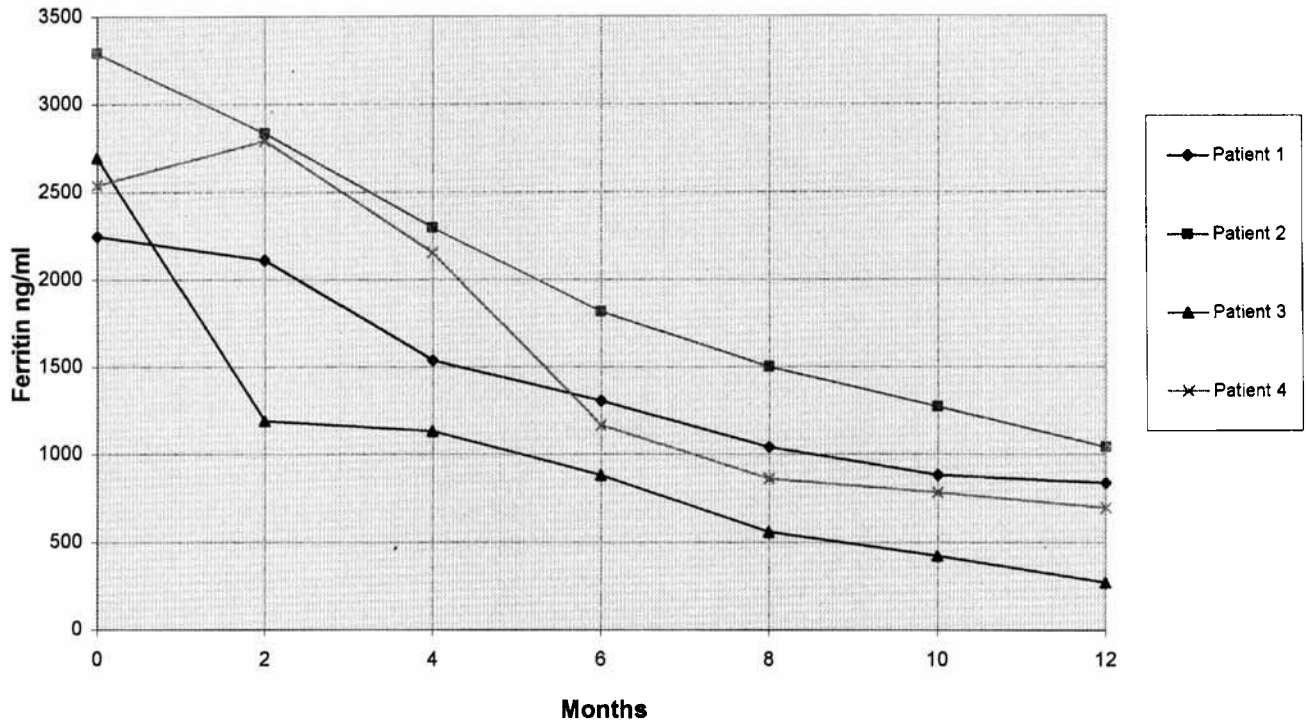

Fig. 1 Serum ferritin levels during intravenous DFO therapy.

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